The phenotype of developmental and epileptic encephalopathy

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Abstract: OBJECTIVE To delineate the electroclinical features of infantile developmental and epileptic encephalopathy (EIEE13, OMIM 614558). METHODS Twenty-two patients, aged 19 months to 22 years, underwent electroclinical assessment. RESULTS Sixteen of 22 patients had mildly delayed development since birth. Drug-resistant epilepsy started at a median age of 4 months, followed by developmental slowing, pyramidal/extrapyramidal signs (22/22), movement disorders (12/22), cortical blindness (17/22), sialorrhea, and severe gastrointestinal symptoms (15/22), worsening during early childhood and plateauing at age 5 to 9 years. Death occurred in 4 children, following extreme neurologic deterioration, at 22 months to 5.5 years. Nonconvulsive status epilepticus recurred in 14 of 22 patients. The most effective antiepileptic drugs were oxcarbazepine, carbamazepine, phenytoin, and benzodiazepines. EEG showed background deterioration, epileptiform abnormalities with a temporo-occipital predominance, and posterior delta/beta activity correlating with visual impairment. Video-EEG documented focal seizures (FS) (22/22), spasm-like episodes (8/22), cortical myoclonus (8/22), and myoclonic absences (1/22). FS typically clustered and were prolonged (<20 minutes) with (1) cyanosis, hypomotor, and vegetative semiology, sometimes unnoticed, followed by (2) tonic-vibratory and (3) (hemi)-clonic manifestations ± evolution to a bilateral tonic-clonic seizure. FS had posterior-temporal/occipital onset, slowly spreading and sometimes migrating between hemispheres. Brain MRI showed progressive parenchymal atrophy and restriction of the optic radiations. CONCLUSIONS developmental and epileptic encephalopathy has strikingly consistent electroclinical features, suggesting a global progressive brain dysfunction primarily affecting the temporo-occipital regions. Both uncontrolled epilepsy and developmental compromise contribute to the profound impairment (increasing risk of death) during early childhood, but stabilization occurs in late childhood.

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ARTICLE

The phenotype of *SCN8A* developmental and epileptic encephalopathy

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Abstract

Objective

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Twenty-two patients, aged 19 months to 22 years, underwent electroclinical assessment.

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Sixteen of 22 patients had mildly delayed development since birth. Drug-resistant epilepsy started at a median age of 4 months, followed by developmental slowing, pyramidal/extrapyramidal signs (22/22), movement disorders (12/22), cortical blindness (17/22), sialorrhea, and severe gastrointestinal symptoms (15/22), worsening during early childhood and plateauing at age 5 to 9 years. Death occurred in 4 children, following extreme neurologic deterioration, at 22 months to 5.5 years. Nonconvulsive status epilepticus recurred in 14 of 22 patients. The most effective antiepileptic drugs were oxcarbazepine, carbamazepine, phenytoin, and benzodiazepines. EEG showed background deterioration, epileptiform abnormalities with a temporo-occipital predominance, and posterior delta/beta activity correlating with visual impairment. Video-EEG documented focal seizures (FS) (22/22), spasm-like episodes (8/22), cortical myoclonus (8/22), and myoclonic absences (1/22). FS typically clustered and were prolonged (<20 minutes) with (1) cyanosis, hypomotor, and vegetative semiology, sometimes unnoticed, followed by (2) tonic-vibratory and (3) (hemi)-clonic manifestations ± evolution to a bilateral tonic-clonic seizure. FS had posterior-temporal/occipital onset, slowly spreading and sometimes migrating between hemispheres. Brain MRI showed progressive parenchymal atrophy and restriction of the optic radiations.

Conclusions:

SCN8A developmental and epileptic encephalopathy has strikingly consistent electroclinical features, suggesting a global progressive brain dysfunction primarily affecting the temporo-occipital regions. Both uncontrolled epilepsy and developmental compromise contribute to the profound impairment (increasing risk of death) during early childhood, but stabilization occurs in late childhood.

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Glossary

AED = antiepileptic drug; **DEE** = developmental and epileptic encephalopathy; **EIEE13** = early infantile epileptic encephalopathy type 13; **FS** = focal seizures; **NCSE** = nonconvulsive status epilepticus; **SUDEP** = sudden unexpected death in epilepsy; **TCS** = tonic-clonic seizure.

SCN8A encodes the pore-forming voltage-gated sodium channel subunit Nav1.6, which is widely expressed in the brain.[1] Pathogenic variants in *SCN8A* result in impaired channel inactivation, causing neuronal hyperexcitability, seizures, and neurocognitive problems.[2]

In humans, pathogenic *SCN8A* variants are associated with a wide spectrum of epilepsy phenotypes, spanning from benign familial infantile seizures[3,4] to mild-to-severe developmental and epileptic encephalopathies.[5–10] Early infantile epileptic encephalopathy type 13 (EIEE13, OMIM #614558) is a recently recognized syndrome caused by de novo *SCN8A* missense variants.[2,11] Clinical features include developmental impairment, which is usually severe, although at times milder, pyramidal and extrapyramidal signs, and epilepsy.[9] Seizures start before 18 months of age and are intractable, although may improve with sodium channel–blocking antiepileptic drugs (AEDs). Multiple seizure types occur, including focal seizures (FS), generalized seizures, and epileptic spasms.[12] In a previous report, we described a heterogeneous spectrum of epilepsies related to variants in *SCN8A* and emphasized the peculiar interictal EEG abnormalities in some patients.[9] SUDEP (sudden unexpected death in epilepsy) is reported in approximately 10% of cases.[2,9,10,13]

Since the same *SCN8A* variant can lead to different clinical scenarios,[13] phenotyping is crucial in informing prognosis. With this study, we sought to further characterize the interictal and ictal electroclinical phenotype in a large homogeneous cohort of patients with severe *SCN8A* developmental and epileptic encephalopathy (*SCN8A*-DEE).

Methods

Through an international collaboration including clinical epilepsy centers in Europe, the United States, and Australia, we collected patients with epileptic encephalopathy due to *SCN8A* variants. Clinical information was collected retrospectively and prospectively by face-to-face interviews with patients and their families and from clinical charts. The referring clinicians provided a detailed phenotyping table, contacting the families in case of missing information.

Neurophysiologic and imaging investigations

Video-EEG recordings were available for 20 of 22 patients at epilepsy onset and all patients at follow-up. EEGs were obtained by a digital acquisition system, placing scalp electrodes according to the 10-20 international system. Selected patients underwent video-polygraphic investigations (EEG, ECG, and EMG traces). In 20 patients, ictal EEG recordings were available, and for the remaining 2 patients, EEG reports were obtained. A single epileptologist with EEG expertise (E.G.) reviewed 97 EEGs (1–12 EEGs per patient, with a follow-up of 10–56 months, including long-term monitoring video-EEGs) for background activity, interictal epileptiform abnormalities, ictal EEG discharges, and clinical manifestations. For 8 patients, an overnight video-EEG was available, and a visual assessment of sleep macrostructure was performed. In selected patients (6, 15, and 17), the interictal and ictal EEG underwent offline analysis, namely, source analysis and dipole localization using the brain electrical source analysis program (BESA GmbH, Gräfelfing, Germany). Electroretinograms, visual evoked potentials, somatosensory evoked potentials, and nerve conduction studies were performed in 4, 7, 4, and 2 patients, respectively. Brain MRI data were obtained from all patients (1–4 scans each), including MRI spectroscopy in 6.

Standard protocol approvals, registrations, and patient consents

Written informed consent, including authorization for reproduction of video images, was obtained for all patients and family members where necessary. Patient data were collected according to guidelines of their country's research ethics committee.

Data availability

Anonymized data that support the findings of this study are available from the corresponding author (E.G.) on reasonable request. Not all of the data are publicly available because they contain information that could compromise children's privacy and their family consent.

Results

We collected the electroclinical data of 17 unpublished and 5 previously published patients. The patients with published data had previously been described in less detail.

The cohort included 11 males and 11 females whose ages ranged from 19 months to 22 years (table 1). None of the patients had a similarly affected family member; however, 6 patients (4, 6, 11, 15, 20, 21) had a family history of epileptic seizures in 1 or 2 first- or second-degree relatives who did not carry an *SCN8A* mutation. All but one (patient 20) were born at term; none had experienced a perinatal insult.

Epilepsy

Median age at epilepsy onset was 4 months (range: 0.5–36 months) (table 1). One child (patient 3) had increased fetal movements, reminiscent of seizures, and one (patient 15) had

Table 1 Clinical findings

		Epilepsy				Motor and cognitive developments				
Pt	Sex/age[a]	Onset	Sz type	Sz duration	Sz frequency/ clusters	Before	After epilepsy onset	Onset/outcome	Epilepsy treatment; (+) effective, (−) not effective	Genetic mutation
1	M/21 y	3 y	T → clon	<20 min	Daily/no	Delay, dystonia	Severe ID, no SP/EC, quadriparesis, dyskinesia	Gradual/(6 y) sz exacerbation, then stable	(+) VPA, CBZ, GVG, CLB, CNZ, LTG, CBZ, ESM; (−) LEV, TPM, FLB, ZNS, PHT, predn	c.1201T>C, p.Tyr401His
2[b]	M/3 y, 10 mo	4 mo	T, Sp	3 s to 1 min	Daily/yes	Delay	Severe ID, no SP/EC, hypotonus, hypokinesia	Gradual/progressive wors	(−) VGB, TPM, CLB, predn, keto diet	c.1228G>T, p.Val410Leu
3[c]	M/(†) 22 mo	1¼ mo	FS	Rarely prolonged	Daily (stretch)/ yes	Severe delay	Severe ID, no SP/EC, EM, dyskinesia, PEG	Stormy/progressive wors until dead	(+) OXC, PHT; (−) multiple AEDs	c.2300C>T, p.Thr767Ile
4	F/25 mo	5½ mo	FS, Sp, TCS	<40 s/SE	Daily to monthly/yes	Hypotonus	Severe ID, no SP/EC, hypotonus, dyskinesia	Acute/poor acquisitions	(+) CLB, OXC, VPA; (−) LEV, TPM, PB	c.2549G>T, p.Arg850Leu
5	M/10 y, 7 mo	1 mo	T, hemiclonic, TCS	30–40 s/SE	Monthly/yes	Hypotonus interm EC	Severe ID, no SP/EC, hypo/ hypertonus, dyskinesia	Stormy/rare sz since age 5 y	(+) CBZ, PHT; (−) LEV, TPM, PB	c.2590C>G, p.Leu864Val
6[b]	F/9 y, 9 mo	2½ mo	FS, Sp, TSC	10 s to 3 min/SE	Monthly to weekly/yes	N	Severe ID, no SP/EC, hypo/ hypertonus, EM, PEG	Stormy/wors until age 6 y, then stable	(+) OXC, TPM, CLB, ZNS; (−) PB, GVG, LEV, predn	c.2879T>A, p.Val960Asp
7	M/27 mo	4 mo	T → clon, Sp, FS, TCS	0.5–2 min/ SE	Daily to monthly/yes	N	Severe ID, no SP/EC, hypotonus, dyskinesia	Stormy/progressive wors	(+) CBZ, TPM, PB, GVG, ACTH; (−) LEV, VPA, PHT	c.2932A>G, p.Ser978Gly
8[b]	F/7 y, 9 mo	10 mo	FS, T, hemiclonic	<60 min/SE	Monthly to weekly/no	Delay	Severe ID, no SP, hypotonus, dyskinesia, PEG	Gradual/progressive wors	(−) VPA, LEV, LTG, OXC, CLB, STP	c.4419+1_+4del, Pro1428_ Lys1473del (pred)
9	M/24 mo	4 mo	T, FS, GTC	1–2 min/SE	Every 3 mo/ yes	Hypotonus	Moderate ID, SP delay, hypotonus dyskinesia, tremor	Stormy/progressive wors, now stable	(+) PHT, CBZ (−) LEV	c.4423G>A, p.GLy1475Arg
10	M/5 y	6 mo	TCS	1–6 min/SE (refractory)	Monthly → now sz-free/ no	N	Moderate ID, motor + SP delay, normal EC, PEG	Gradual/better from age 5 y	(+) PB, OXC, LCS, CLB; (−) LEV, ZNS, VPA	c.4423G>A, p.Gly1475Arg
11	F/3 y, 9 mo	4½ mo	Asym T → clon	2 min/ subsequent sz	Daily → now sz-free/no	N/mild delay	Moderate/severe ID, no SP, interm EC, progr microcrania	Stormy/progressive wors	(+) CBZ CLB, GVG, TPM, predn, keto diet; (−) LEV, VPA	c.4423G>A, p.Gly1475Arg
12	F/19 mo	3 wk	T	3–5 min/SE	Monthly/yes	Hypotonus	Severe ID, no SP/EC, hypo/ hypertonus	Stormy/severe drug-resistant epilepsy	(+) PHT, MDZ (SE); (−) CBZ, LZP, VPA, LEV, LCS, PB, CBD	c.4472C>T, p.Ala1491Val
13	M/(†) 26 mo	1 mo	T, TCS	2 min/SE	50–200 d → monthly/yes	Delay	Severe ID, no SP/EC, hypotonus, PEG	Stormy/progressive wors	(+) LCS; (−) PB, PHT, LEV, OXC, TPM, CBD, keto diet	c.4472C>T, p.Ala1491Val
14	F/15 y, 10 mo	2 mo	FS, MA, clon, TCS	5 s to 2 min/ SE	Weekly/no	Delay	Severe ID, no SP, good EC, EM	Stormy/wors until age 9 y, then stable	(+) STP, keto diet	c.4493A>T, p.Lys1498Met

Continued

Table 1 Clinical findings *(continued)*

		Epilepsy				Motor and cognitive developments				
Pt	Sex/age[a]	Onset	Sz type	Sz duration	Sz frequency/ clusters	Before	After epilepsy onset	Onset/outcome	Epilepsy treatment; (+) effective, (−) not effective	Genetic mutation
15	F/3 y, 10 mo	3½ mo	FS, Tv, Sp, TCS	2–8 min	Monthly/yes	N (jerks)	Severe ID, no SP/EC, EM, hypo/ hypertonus, dyskinesia, PEG	Stormy/regression and progressive wors	(+) TPM, VPA, CLB, STP, PB, ESM, CLN, CBZ, PHT; (−) CNZ, CLB, predn	c.4594A>T, p.Ile1532Phe
16	M/22 y	15 d	FS, T, Sp, TCS	few s to 2 min/SE	Monthly/yes	N (lateral eye movement)	Severe ID, no SP/EC, EM, hypotonus, dyskinesia	Stormy/wors until age 7 y, than ↓ sz freq	(+) VPA, PB, VGV, PHT, TPM, LTG, NZP, FBM, ZNS, RFM, keto diet	c.4639T>G, p.Phe1547Val
17[b]	F/(†) 23 mo	5½ mo	FS, TCS	3–15 min/SE	Monthly/yes	N	Severe ID, no SP/EC, EM, hypotonus, dyskinesia	Gradual/progressive wors until dead	(+) VPA, CNZ, ZNS, ETS, TPM; (−) LTG, LEV, keto diet	c.4850G>A, p.Arg1617Gln
18[c]	F/8 y	3 mo	Asym T/Tv, FS, TCS	1–2 min/SE	Several per day → monthly/yes	Hypotonus	Severe ID, interm EC, no SP, hypo/hypertonus, dyskinesia, PEG	Stormy/wors until 5 y, then stable	(+) CBZ, PHT, PRM, predn; (−) LEV, LCS, STP, PB, TPM, ZNS, keto diet	c.4948G>A, p.Ala1650Thr
19[c]	F/9 y	4 mo	FS, TCS	5–10 min/SE	Several per day/yes	Delay	Severe ID, no SP/EC, quadriparesis, dyskinesia	Gradual/progressive wors	(+) CBZ, PB, VPA, PRP, CLB, predn, LCM, keto diet; (−) LEV	c.4948G>A, p.Ala1650Thr
20	M/15 y	11½ mo	T, Tv → clon	s to 10 min/ SE	Weekly/yes	Hypotonus dystonia	Moderate/severe ID, no SP, poor EC, dystonia, EM, hypotonus, microcrania	Stormy/wors until age 7 y, then stable	(+) PHT, CLB, DZP, predn	c.5292C>G, p.Ile1764Met
21[b]	F/(†) 5 y	4 mo	FS, asym T/ Tv, Sp, TCS	<40 min/SE	Monthly/yes	N	Severe ID, no SP/EC, EM, PEG	Stormy/progressive wors until dead	(+) PB, VPA, LTG, TPM, CLB, OXC, DZP, keto diet; (−) LEV, RFM	c.5614C>T, p.Arg1872Trp
22[c]	M/2 y, 9 mo	3 mo	FS → T, TSC	<20 min	Daily/no	Mild delay	Moderate/severe ID, no SP, progressive microcrania	Stormy/progressive wors	(+) TPM, VPA, PHT, CLB, STP, PB, ESM, CLN, CBZ	c.5614C>T, p.Arg1872Trp

Abbreviations: ACTH = adrenocorticotropic hormone; AEDs = antiepileptic drugs; asym = asymmetric; CBD = cannabidiol; CBZ = carbamazepine; CLB = clobazam; clon = clonic; CNZ = clonazepam; EC = eye contact; EM = epileptic myoclonus; ESM = ethosuximide; freq = frequency; FLB = felbamate; FS = focal seizure; GVG = gamma-vinyl GABA; ID = intellectual disability; interm = intermittent; keto = ketogenic; LEV = levetiracetam; LTG = lamotrigine; MA = myoclonic absences; N = normal; PEG = percutaneous endoscopic gastrostomy feeding tube; PHT = phenytoin; predn = prednisolone; PRP = perampanel; pt = patient; SE = status epilepticus; Sp = spasm-like episodes; SP = speech language; STP = stiripentol; sz = seizures; T = tonic; TCS = tonic-clonic seizures; TPM = topiramate; Tv = tonic vibratory; VPA = valproic acid; wors = worsening; ZNS = zonisamide.

[a] Age at latest investigation.

[b] Larsen et al., 2015.

[c] Same patient described in references 8 and 15 (no clinical information reported).

† Deceased.

myoclonic jerks from birth. The most common seizure types at epilepsy onset were tonic, tonic-vibratory, and tonic-clonic (18/22), often asymmetric or lateralized (7/22), and preceded by cyanosis or autonomic features (9/22). One patient (7) had nonconvulsive status epilepticus (NCSE) at epilepsy onset. Two patients debuted with subsequent "convulsive" afebrile seizure (15, 22) and 2 had epileptic spasms with hypsarrhythmia at onset (2, 4).

Over the course of the disease, all patients developed motor and nonmotor FS including focal to bilateral tonic-clonic seizures (TCS) (17/22), spasm-like episodes (8/22 [36%]), and erratic myoclonus (8/22 ([36%]). In 18 of 22 patients (82%), seizures were prolonged (up to 20 minutes), often requiring acute benzodiazepine administration, and, in some cases, resuscitation because of severe oxygen desaturation (9, 19, 22). In 16 of 22 patients (73%), seizures clustered over 2 to 3 days (table 1), often ending with one or more generalized TCS. Seizures occurred most often during sleep; this was very frequently reported from children's caregivers and from clinical charts. In 8 patients, this finding was confirmed by prolonged video-EEG recordings, including all-night sleep. According to the clinical reports, seizures might have also been exacerbated during febrile/afebrile illness in 7 patients (31%) (4–6, 15, 17, 20, 22) and after sleep deprivation or on (provoked) awakening in 4 (18%) (1, 15, 18, 22). Fourteen patients (64%) had episodes of NCSE, in 7 of them with myoclonic features. In 2 patients (7 and 12), NCSE was drug-refractory and followed by severe worsening of the neurologic status.

Epilepsy was poorly controlled in all but 4 patients (5, 9, 10, 11) despite combinations of 2 to 3 AEDs and trials of 3 to 14 AEDs per patient. The most effective AEDs were phenytoin, carbamazepine, and oxcarbazepine (table 1), usually at supratherapeutic doses. Benzodiazepines (clobazam, diazepam, midazolam) were effective in halting seizure clusters in 15 of 22 children (68%). Levetiracetam was tried in 15 patients, with poor effect, if any, in 13 patients and seizure exacerbation in 2. Inconsistent seizure improvement was observed with other sodium channel blockers (lamotrigine, effective in 3/5 patients; topiramate effective in 8/14 patients). Zonisamide was effective in 5 of 6 patients (6, 10, 16, 17, 18). Single patients experienced transient benefit on stiripentol (3/5 children; in patient 14, for generalized TCS), lacosamide (1/3 children; patient 10), rufinamide (patients 16 and 21), and perampanel (patient 18). In one patient (16), felbamate exacerbated his movement disorders. Spasms improved on high-dose prednisolone/adrenocorticotropic hormone (8/8 patients, lost efficacy in 4 of them) and vigabatrin (4 patients). One patient (4) had severe hypotonia, respiratory insufficiency, and somnolence on prednisolone and vigabatrin, with no benefit for her spasms. The ketogenic diet was effective in 5 patients (used acutely to stop NCSE in patient 14); no improvement was observed in 4. Cannabidiol was tried in 2 children (12, 13) without benefit.

Other neurologic findings

Sixteen patients (73%) had mild to moderate developmental delay since birth. Other neurologic signs (table 1) predated epilepsy onset in 5 patients (23%) (1, 5, 15, 16, 20). Epilepsy onset was associated with cognitive decline in all. Twenty of 22 children (91%) had severe to profound intellectual disability when last seen. Speech was absent in 20 patients (91%) and delayed in 2 patients (9, few words; 10, simple sentences). Seventeen patients (77%) developed progressive cortical visual impairment, initially intermittent in relation to seizure clusters, and nystagmoid eye movements. Other common neurologic features included axial hypotonia (14 patients [64%]), quadriplegia/limb spasticity (11 patients [50%]), extrapyramidal or cerebellar signs (dystonia, choreoathetosis, dyskinesia, clumsiness, poor coordination) (12 patients [55%]), and myoclonus (8 patients [36%]). Four patients (18%) developed progressive microcephaly (11, 20, 22) or decelerating head growth velocity (4). One child (5) had intermittent nonepileptic diaphragmatic myoclonus. Gastrointestinal disorders were reported in 18 of 22 patients (82%), ranging from sialorrhea (3 patients) to severe gastroesophageal reflux, constipation, and inadequate or unsafe oral feeding (15 patients). Eleven children (50%) required a percutaneous endoscopic gastrostomy feeding tube. Spontaneous bone fractures were reported in 2 patients (9%) (16 and 20). Dysmorphic features were not observed.

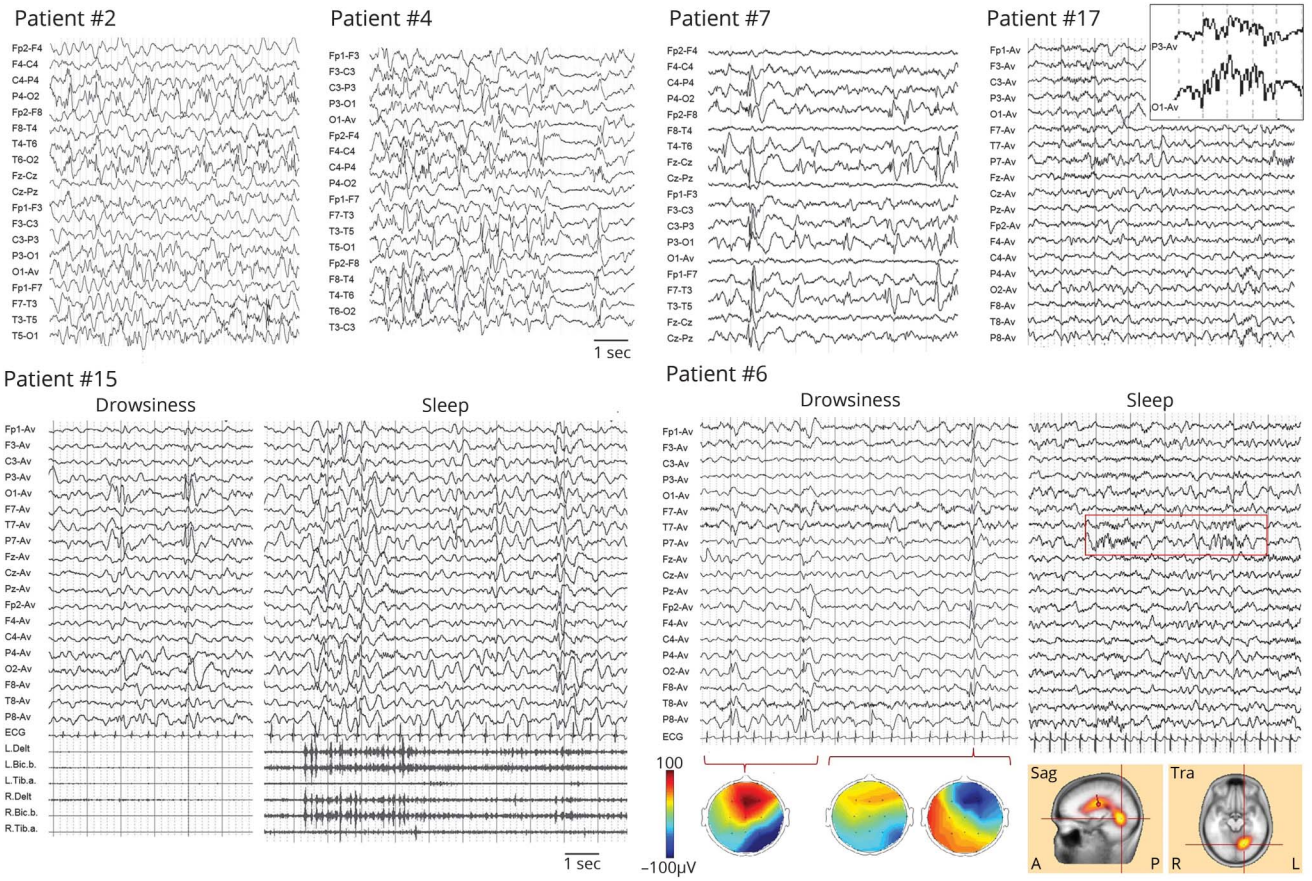
Epilepsy, cognitive decline, and neurologic signs had a stormy onset and progressive worsening in 16 of 22 patients (73%). The remaining 6 children (27%) followed a more gradual course, with periods of stagnation and regression associated with increased seizure frequency, alternating with partial recovery during seizure-free periods.

Four patients (18%) (3, 13, 17, 21) died between age 22 months and 5 years 6 months. Before dying, all 4 had uncontrolled seizures and progressive severe neurologic deterioration; 3 succumbed to a lower respiratory tract infection (3, 13, 21). Patient 17 died in a terminal phase of her disease, after extreme worsening of her epilepsy and general condition the last year of life. Among older patients, aged 6–22 years (10/22), 8 stabilized or improved overall with age, with better seizure control, from age 5 to 9 years. One child (9), with stormy epilepsy onset at the age of 4 months, showed a milder evolution from 2 years of age.

EEG and other neurophysiologic investigations

Interictal EEG at epilepsy onset was normal in 7 of 20 patients (35%), showed discrete slowing and infrequent epileptiform abnormalities in 10 (40%), hypsarrhythmia in 2, and NCSE in one. All patients developed progressive background slowing and multifocal epileptiform abnormalities, occurring asynchronously, predominantly in the temporo-parieto-occipital regions, either at epilepsy onset (6/20 [30%]) or after 1 to 7 months (14/20 [70%]). EEG abnormalities consisted of high-amplitude sharp waves and trains of delta and beta activity, increased during sleep (figure 1). The progressive increase of posterior temporo-occipital beta/delta activity paralleled worsening of visual impairment. Source analysis indicated

Figure 1 Interictal EEG



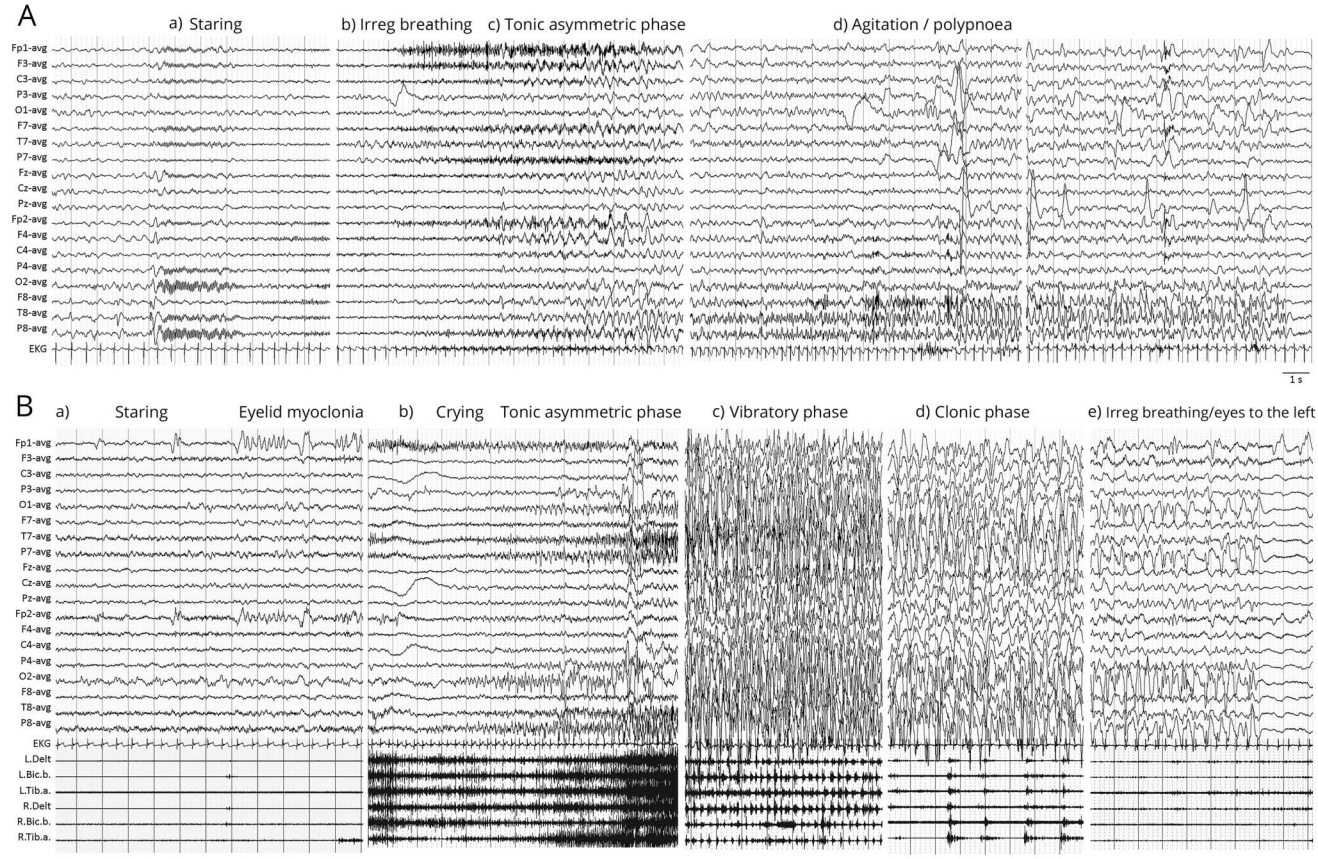
Interictal EEG of patients 2 (15 months), 4 (18 months), 7 (8 months), 17 (23 months), 15 (10 months), and 6 (23 months) showing common features of (1) background slowing, (2) blending of polymorphic delta and beta activity (18–20 Hz), usually in trains of 200–600 milliseconds (see patient 17), and (3) multifocal spike and waves, predominant in the posterior temporal and parieto-occipital regions bilaterally asynchronously. Patient 15: Both beta activity and the epileptiform abnormalities have an accentuation and diffuse spreading during sleep. Concomitantly with the anterior spreading of the epileptiform abnormalities, discrete rhythmic myoclonic jerks (7–8 Hz) appeared. EEG parameters: sensitivity 100 μV/mm, band-pass filter 1–70 Hz. Patient 6: Discrete, subcontinuous beta and delta activity and spike/polyspikes-and-waves in the right posterior temporo-occipital regions or diffuse, with frontal predominance, but posterior onset, as shown on the amplitude maps below the EEG. The source analysis of the beta activity (below the EEG trace) indicated a generator deep in the occipitoparietal regions. EEG parameters: sensitivity 150 μV/mm, band-pass filter 1–50 Hz.

a generator deep in the occipitoparietal regions (figure 1). An overnight sleep EEG was recorded in 10 patients, revealing a regularly organized sleep macrostructure.

Seizures were captured on video-EEG in 21 of 22 patients. FS were the most common seizure type. We did not record any true generalized TCS, only focal-to-bilateral TCS, and the reported "absence" seizures were all FS, except for patient 14, who had myoclonic absences from age 10 months. FS were typically prolonged, lasting up to 20 minutes, with (1) prominent hypomotor and autonomic symptoms (flushing, tachycardia, and/or bradycardia), often with lateral eye deviation, mouth or eyelid myoclonia, apnea, and cyanosis, followed at times by (2) asymmetric tonic or tonic-vibratory phase and (3) prolonged clonic or hemiclonic manifestations with or without (4) bilateral TCS (figure 2 and video 1). The hypomotor phase, which often passed unnoticed, could lead directly to a bilateral TCS. The EEG correlate of FS showed 2 spread patterns: (1) posterior temporal rhythmic activity (at seizure onset and end), with slow spread sometimes with intraictal migration from one hemisphere to the other or, less frequently, (2) diffuse EEG desynchronization, followed by posterior rhythmic spiking and spreading to the frontocentral regions (figure 2).

In 7 children (32%), we documented episodes resembling spasms, often asymmetric and followed by hyperkinetic manifestations (5–10 seconds) (video 2). They were recorded during both wakefulness and sleep, occurring independently or in clusters after an FS. The EEG correlate was diffuse low-voltage fast activity, sometimes preceded by a high-voltage sharp and slow wave complex, consistent with a tonic seizure pattern (figure 3A). Seven patients (32%) had segmental erratic jerks, consistent with cortical myoclonus, often occurring almost continuously (figure 1). Two patients also had tongue (3) and laryngeal myoclonus (16). In 5 patients, we recorded myoclonic NCSE, with an EEG correlate consisting of triphasic sharp waves predominant in the central or rolandic regions (figure 3B). Two children had

Figure 2 Ictal EEG



(A) Patient 6 (23 months): subtle focal seizure (duration: 1′15″) during sleep, with polypnea, and tachycardia, tonic asymmetric posturing (right arm flexed), eye deviation to the right, discrete flushing, and blinking. This EEG shows a right occipital and posterior temporal onset and propagation. Clinical manifestations: (a) Staring, (b) Irregular breathing, (c) Tonic asymmetric phase, (d) Agitation/polypnoea. EEG parameters: sensitivity 150 μV/mm, band-pass filter 1.6–50 Hz. (B) Patient 15 (10 months): prolonged tonic-vibratory and clonic seizure during sleep with subtle, unrecognized onset (duration: ca. 4′50″). Clinical manifestations: (a) arousal and staring, mild polypnea (ca. 1′) followed by frequent blinking and eyelid myoclonia (ca. 50″), (b) deviation of head and eyes to the left and asymmetric tonic posturing (right arm flexed) (18″), then crying and (d) clonic-vibratory phase (ca. 35″) and (d) clonic jerks. The seizure ends with staring eye deviation to the left, eyelid myoclonia, and irregular breathing and chewing (d). During the first part of the seizure (a), the EEG shows only a discrete slowing in the right posterior quadrant (maximum occipital), evolving into posterior rhythmic rapid activity (right > left) (b) and diffuse spike-and-slow waves (c and d). The seizure ends focally in the occipital and posterior temporal regions (e). EEG parameters for (A) and (B): sensitivity 150 μV/mm, band-pass filter 1.6–50 Hz. These seizures are shown in video 1.

recurrent paroxysmal autonomic manifestations with hyperventilation, sweating, tachycardia (patient 3), or change of pupil size (patient 4), without EEG correlate.

Electroretinograms were normal in 4 of 5 cases (11, 12, 16, 21) and low amplitude in one (7). Visual evoked potentials were normal in 4 patients (1, 6, 12, 16), showed reduced amplitude in 2 (7, 18), and increased latency in 2 (7, 14). Somatosensory evoked potentials were normal in 3 patients (1, 6, 11) and extinct in one (14). Sensory and motor nerve conduction studies in 2 children (5, 8) were normal.

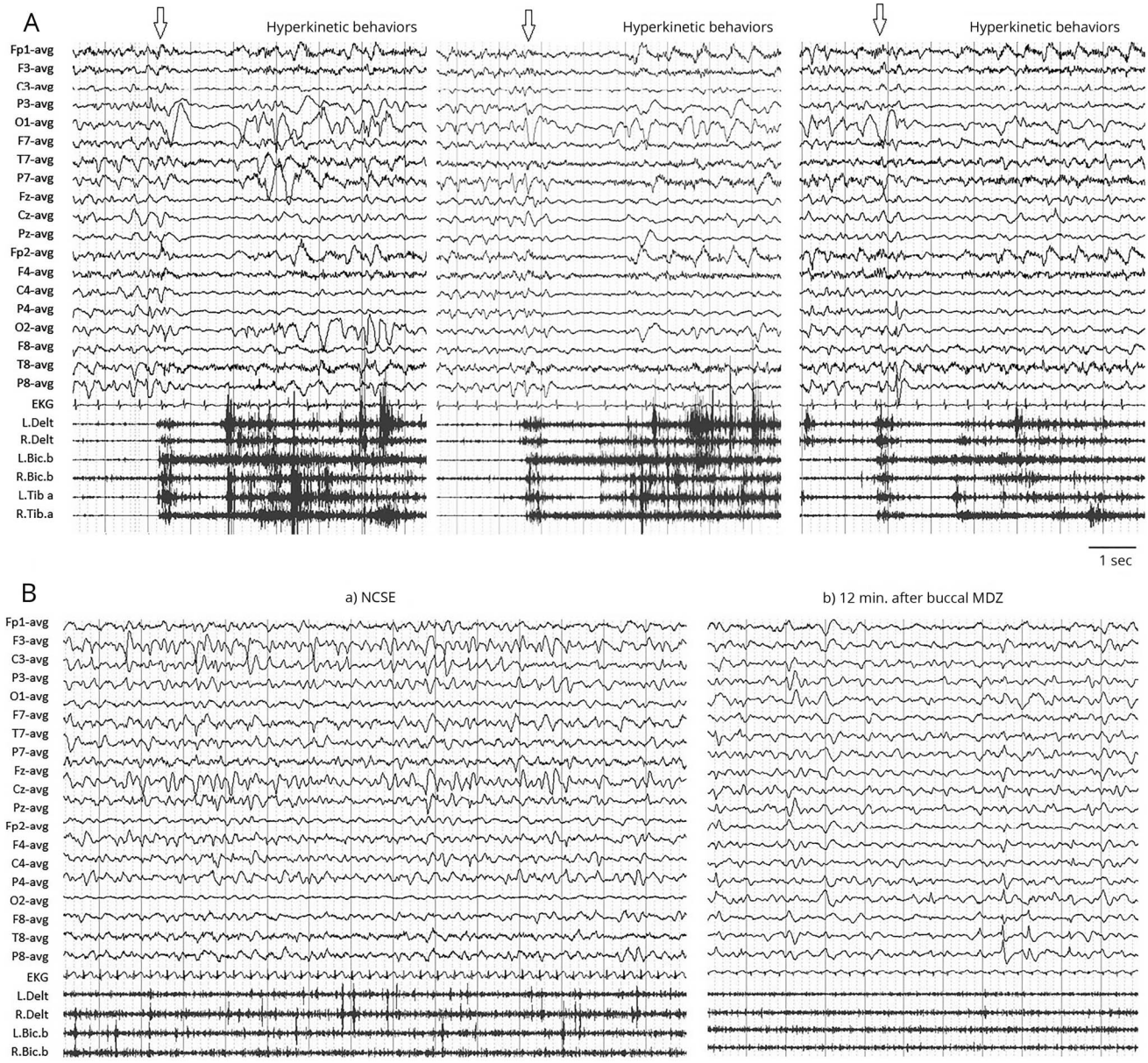
MRI findings

In 20 of 22 patients (91%), cerebral MRI was normal or showed minor abnormalities at epilepsy onset. Two (13, 21) had mild brain atrophy at age 10 months. In 10 patients (45%) (1, 3–7, 10–12, 16), follow-up MRI scans showed progressive cortical and subcortical atrophy (figure 4, patient 3). One patient (4) had sequelae of a choroid plexus and cerebellar hemorrhage. In 3 patients (3, 4, 16), hyperintensity of the posttrigonal white matter on T2-weighted imaging was seen, along with restricted diffusion in the optic radiations (figure 4, patients 4 and 16). Magnetic resonance spectroscopy was abnormal in 2 of 6 patients, showing nonspecific posterior abnormalities (patient 7) or a reduced *N*-acetylaspartate/creatine ratio, and increased choline/creatine ratio in the parietal retroventricular white matter, likely due to cell membrane turnover (figure 4, patient 16).

Genetic investigations

Twenty-one of 22 patients (95%) carried a de novo heterozygous missense variant in *SCN8A* (table 1). We identified 16 different missense variants; all were predicted to be damaging by one or more prediction tools (PolyPhen-2, SIFT, MutationTaster) and absent in control databases (ExAC, gnomAD). Patient 8 carried a de novo splice-site variant, predicted to cause the inframe deletion Pro1428_Lys1473del and absent in control databases (ExAC, gnomAD). The splice-site variant and 9

Figure 3 Episodes resembling spasms, and myoclonic NCSE



(A) Video-EEG-polygraphic recordings in patient 6 (6 years, 6 months), showing a cluster of episodes resembling spasms, followed by mild hyperkinetic behaviors, corresponding to diffuse EEG flattening followed by discrete slowing in the occipital regions. These polygraphic recordings correspond to the spasm-like events shown in video 2. EEG parameters: sensitivity 300 μV/mm, band-pass filter 1.6–50 Hz. (B) EEG-polygraphic recordings in patient 21 (4 years, 1 month) showing (a) accentuation of the myoclonus and perturbation of consciousness for several hours, consistent with myoclonic NCSE. The EEG shows continuous rhythmic activity with superimposed high-amplitude sharp waves, in the left fronto-central region and the vertex. (b) After benzodiazepine (buccal midazolam [MDZ]): resolution of the symptoms and reappearance of the interictal epileptiform abnormalities in the temporo-parieto-occipital region. EEG parameters: sensitivity 300 μV/mm, band-pass filter 1–70 Hz. NCSE = nonconvulsive status epilepticus.

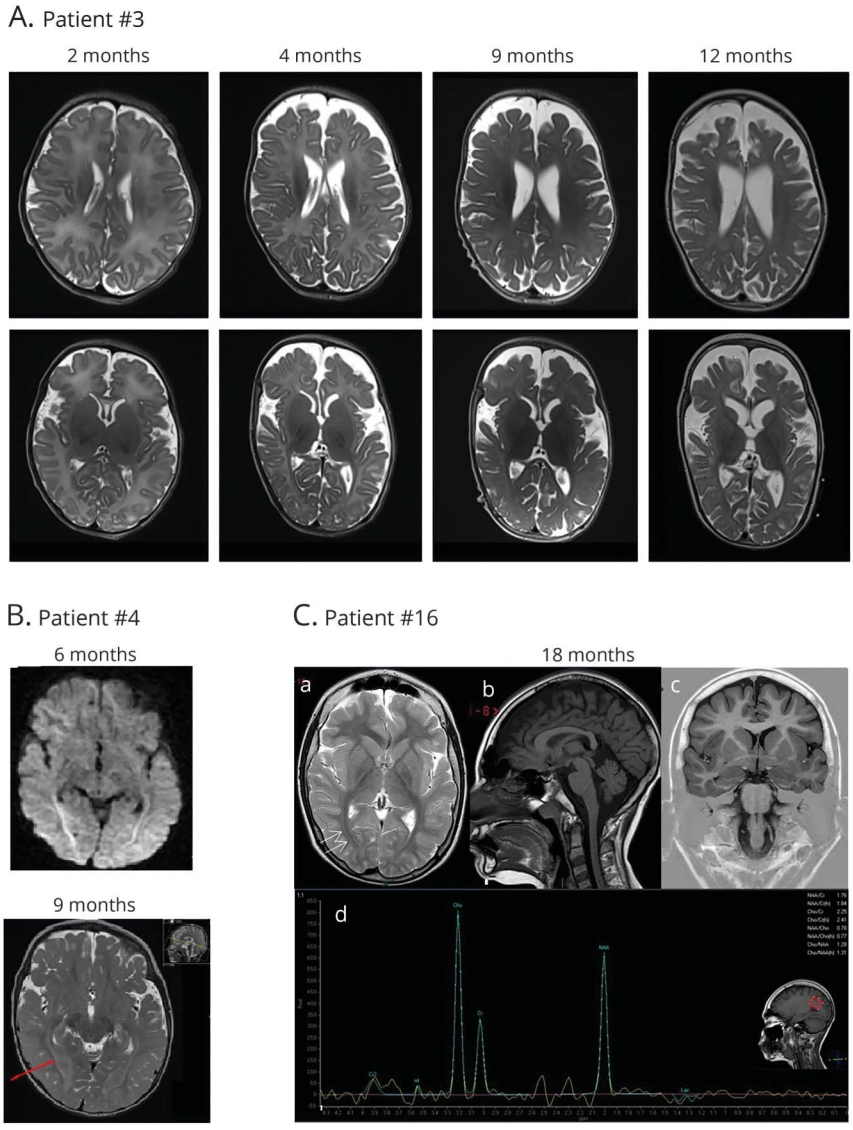
of the missense variants have been previously published.[8,9,14–16] Seven missense variants (p.Tyr401His, p.Arg850Leu, p.Leu864Val, p.Ala1491Val, p.Lys1498Met, p.Phe1547Val, p.Ile1764Met) have not been previously reported (figure 5).

Discussion

We report a description of the phenotype of EIEE related to de novo heterozygous variant in *SCN8A* (EIEE13, OMIM #614558).

Twenty-one of 22 patients had a missense variant, whereas one (previously published) patient had a de novo splice-site variant, whose predicted product is a frame deletion. Seven missense variants have not previously been associated with *SCN8A*-DEE, 5 of them being located into domains relevant to protein function (figure 4). Nine of the missense variants[17] have been previously described.[8,9,14–16] However, 4 patients with these mutations are unpublished (3, 18, 19, 22). Four missense variants recurred in 2 to 3 patients each in the present study (p.GLy1475Arg, p.Ala1491Val, p.Ala1650Thr, p.Arg1872Trp).

Figure 4 MRI findings



(A) Patient 3: Axial T2-weighted MRI showing progressive cortical and subcortical brain atrophy from age 2 to 12 months. (B) Patient 4: Axial T2-weighted MRI showing mild frontotemporal atrophy, hyperintensity (arrow), and progressive restriction in optic radiations from age 6 to 9 months. (C) Patient 16: Axial T2-weighted (a), sagittal T1-weighted (b), coronal inversion recovery (c), and single voxel spectroscopy study (d) at echo time = 144 milliseconds in the left posterior hemispheric white matter. Conventional MRI (a, b, c) shows frontal lobe hypoplasia (a, b), hypoplasia of the posterior segment of the corpus callosum (b), mainly at the level of the splenium and of the vermis (b). Dysmorphism/dysplasia of the mesial temporal regions is also evident (c), predominantly on the left side, as well as linear medial hyperintensity of the pallidi (a) of uncertain significance. Magnetic resonance spectroscopy (d) shows reduced *N*-acetylaspartate (NAA)/creatine (Cr) ratio, due to aspecific neuroaxonal damage, and increased choline (Cho)/Cr ratio, likely due to cell membrane turnover.

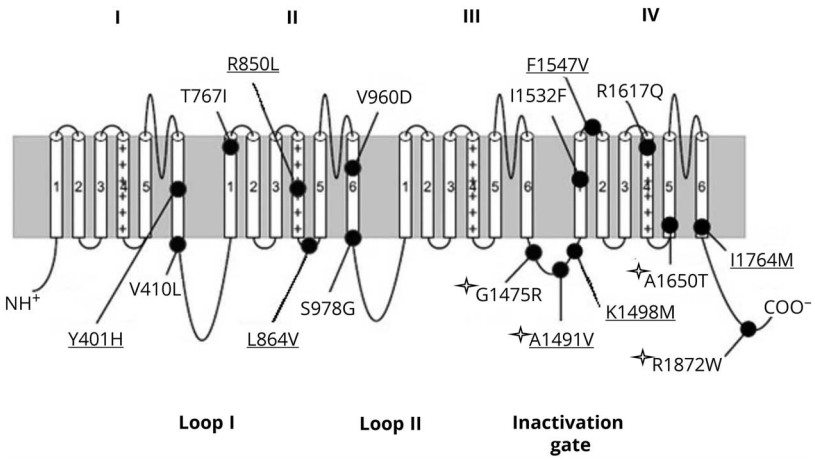
We could not find evident genotype-phenotype correlations, both among the present group of patients and compared with the benign cases previously described.[3]

From birth, 73% of patients had developmental delay and/or other neurologic signs (23%). Epilepsy onset, at a median age of 4 months (range 1–36 months), was typically stormy (73%), but a more gradual and progressive course was also seen (27%). The finding of rhythmic fetal or neonatal abnormal movements in 2 children suggested a possible prenatal subtle onset of epilepsy or movement disorder.[18]

The interictal EEG was normal or mildly abnormal in 91% of patients at epilepsy onset, then deteriorated, as observed previously,[9] recapitulating the murine model (heterozygous *Scn8a*$^{N1768D/+}$ mice).[19] Despite the severe evolution of the disease, the interictal EEG was often normal or almost normal for several months after epilepsy onset.[20] With time, multifocal interictal epileptiform discharges, predominantly in the posterior quadrants, together with progressively increasing delta activity with superimposed bursts of beta activity appeared, as observed previously.[9] This peculiar EEG pattern (figure 1) has not been reported in *SCN2A*-related epileptic encephalopathy and differs from EEG abnormalities in epilepsy syndromes within the generalized epilepsy with febrile seizures plus spectrum with *SCN1A* mutations,[21] and might be a marker of EIEE13.

The source analysis of the beta-delta activity suggests a generator deep in the occipitoposterior temporal regions. In a few patients with cortical visual impairment, the MRI showed a restriction and hyperintensity of the visual tract and the magnetic resonance spectroscopy an alteration at the level of the retroventricular white matter, reflecting neuroaxonal damage and abnormal cellular membrane turnover, as in the

Figure 5 Gene structure and position of pathogenic variants



Four-domain structure of the voltage-gated sodium channel α subunit, with transmembrane segments 1–4 forming the voltage sensor domain and segments 5 and 6 forming the pore region with its pore-forming loop. The inactivation gate is located between transmembrane domain 3 and 4. All the pathogenic variants identified in this study are indicated, and the 7 novel variants are underscored: p.Ala1491Val (patients 12 and 13) and p.Lys1498Met (patient 14) affect the inactivation gate, p.Tyr401His (patient 1), p.Ile1764Met (patient 20) affect the transmembrane segment S6 of the DI and the DIV, respectively, essential to form the intracellular mouth of the pore, and p.Arg850Leu (patient 4) placed in the S4 helix of the DII, involved in voltage sensitivity, p.Leu864Val (patient 5) and p.Phe1547Val (patient 16) are located in highly conserved regions of the gene. The recurrent mutations (founded in 2–3 patients with *SCN8A* developmental and epileptic encephalopathy [references 8 and 9 and the present report]) are marked with a star.

case of demyelination and gliosis (figure 4, patients 4 and 16). Likewise, in infants with perinatal brain lesions and in children with West syndrome, the visual impairment correlates better with the EEG than with the brain MRI findings.[22,23]

In contrast to the description of a disturbed sleep pattern in the homozygous null mice lacking functional NaV1.6,[24] we failed to document alterations of sleep macrostructure. The disease mechanisms of the homozygous loss-of-function mice are probably different from the heterozygous, likely gain-of-function pathogenic variants in our patients.

Video-EEG recordings documented FS with posterior EEG onset and slow spreading, sometimes with intraictal migration of the epileptic discharge from one hemisphere to the other. The early clinical semiology included (1) hypomotor and autonomic symptoms, eye deviation, and often cyanosis, eventually evolving to (2) asymmetric tonic and (3) (hemi)-clonic manifestations with or without (4) bilateral TCS. All recorded TCS were focal onset seizures that became bilateral; in some cases, seizure onset was not recognized. FS were often misclassified as absences, tonic, or generalized tonic-clonic seizures, or even unrecognized, depending on the prominence of motor manifestations. True myoclonic absence seizures were recorded in only one patient (14). The mouse model of *SCN8A*-related epilepsy exhibits diffuse spike-waves and absence epilepsy, suggesting that *SCN8A* might cause generalized epilepsy as well.[25] Children with *SCN8A*-DEE have been reported as having both FS and generalized seizures.[8,9] Here, we classified seizures based on video-EEG recordings, documenting focal to bilateral TCS, without true generalized TCS. We therefore conclude that *SCN8A*-DEE presents as a (multi)focal encephalopathy rather than a generalized one. In a few patients, we observed intraictal migration of the FS from one hemisphere to the other, similar to what is observed in *SCN2A* encephalopathy.[26] FS were characterized by posterior temporo-occipital onset and offset, very long duration (several minutes), and clustering. NCSE was also common (64%), often having a myoclonic component. These features have not been previously described and might be characteristic of, although not specific to, *SCN8A*-DEE.

Cortical myoclonus (36%) and clusters of spasm-like episodes (36%) (figure 3) were relatively common features in *SCN8A*-DEE. This is recapitulated in the mouse model of *SCN8A*-DEE that shows diffuse spike- or polyspikes-and-slow wave discharges, often accompanied by spasms or myoclonic jerks.[19]

All seizures were extremely drug-resistant, with only 2 patients achieving periods of seizure control. The most effective AEDs were phenytoin, carbamazepine, and oxcarbazepine, usually at supratherapeutic doses. Both seizure clusters and NCSE were responsive to benzodiazepines. Levetiracetam was constantly ineffective or even worsened seizures. The ketogenic diet was somewhat effective in 5 of 9 patients (55%), and in one patient succeeded in interrupting refractory NCSE. Thus, the ketogenic diet, effective in 75% of patients with Dravet syndrome,[27] is also valuable in *SCN8A*-DEE. Steroids provided some benefit acutely and for control of spasms. Cannabinoids were tried in 2 children, with no effects.

In all patients, seizure onset was followed by developmental regression, with eventual severe to profound intellectual disability, absent speech (91%), worsening pyramidal/extrapyramidal signs, dystonia and choreoathetosis (55%), progressive visual impairment resulting in cortical blindness (77%), and severe gastrointestinal problems (68%) with enteral feeding (45%). Progressive microcephaly and spontaneous bone fractures were occasionally reported. Recently, bone loss syndrome with elevated bone reabsorption has been associated with *SCN8A*-DEE.[28] These clinical features are distinguishable from most of the other common genetic

Table 2 Electroclinical features of the most frequent genetic causes of developmental and epileptic encephalopathies

Mutation	Phenotypes (median age at onset)	Mutation type (function)	Seizure type	EEG features	Cognition	Other neurologic features	Sz outcome (most effective AEDs)	Additional features	Other associated phenotypes
SCN8A **(present report, Larsen et al.,[9] 2015)**	Severe DEE (4 mo); Milder epilepsy (<1 y)	Missense (GOF)	F (aut feat) + EM + Sp + TCS/clusters	BG slowing, posterior delta/beta activity and SW	Severe ID	Quadriplegia, cortical blindness, dyskinesia, ataxia	Drug-resistant (CBZ, OXC, VPA)	Dysphagia (PEG), cortical blindness, spontaneous fractures	BFIS/ICCA ID, ASD
SCN1A **(Bureau and Dalla Bernardina,[21] 2011) (Sadleir et al.,[33] 2017)**	Dravet sd; EOEE	Missense/ truncating (LOF)	Hemiclonic (alternating) + F + AA + TCS + febrile seizures	BG slowing, theta vertex/rolandic reg diff polySW (max FC)	Moderate ID; Severe-profound ID	Hypotonia, ataxia, crouch gait	(VPA, CLB, STP, TPM, keto diet, CBD, fenfluramine); Sodium channel blockers to be avoided	Autistic features, ADHD, SUDEP	GEFS+, familial migraine
SCN2A **(Wolff et al.,[29] 2017)**	EOEE, Ohtahara sd (<3 mo); EIMFS (>3 mo)	Missense (GOF); Missense/ truncating (LOF)	F + Sp; F (aut feat) + Sp + T + hemiclonic	BG slowing, multifocal epileptiform abn, ESES-like pattern	Severe ID	Hypotonia, ataxia	Sz-free/reduction (PHT, OXC, CBZ); Drug-resistant	Dysphagia (PEG)	BFIS, ASD, MAE, ESES-like
STXBP1 **(Stamberger et al.,[34] 2016)**	EOEE (6 wk); Otahara sd →; West sd, Dravet sd	Truncating/ missense (LOF)	Sp + F + T	Burst-suppression pattern, hypsarrhythmia	Severe to profound ID	Pyramidal, extrapyramidal, cerebellar signs, dyskinesia	33% patients sz-free (VPA, LEV, GVG)	Autistic features	ID, ASD
KCNQ2 **(Weckhuysen et al.,[35] 2012)**	EOEE (neonatal <3 mo)	Missense (GOF)	T (apnea) + clon + EM + Sp + TCS	BG slowing, multifocal epileptiform abn	Mild to profound ID	Hypo/hypertonus, dystonic fits	Variable degree of drug resistance (CBZ, PHT)	Ictal bradycardia, SUDEP	BFNS

Abbreviations: AA = atypical absences; abn = abnormalities; ADHD = attention-deficit/hyperactivity disorder; AEDs = antiepileptic drugs; ASD = autism spectrum disorders; aut feat = autonomic features; BFIS = benign familial infantile seizures; BFNS = benign familial neonatal seizures; BG = background; CBD = cannabidiol; CBZ = carbamazepine; CLB = clobazam; clon = clonic; DEE = developmental and epileptic encephalopathy; Diff = diffuse; EIMFS = epilepsy of infancy with migrating focal seizures; EM = epileptic myoclonus; EOEE = early-onset epileptic encephalopathy; ESES = encephalopathy with status epilepticus during sleep; F = focal seizures; FC = fronto-central; GEFS+ = generalized epilepsy with febrile seizures plus; GOF = gain of function; GVG = gamma-vinyl GABA; ICCA = infantile convulsions and paroxysmal choreoathetosis; ID = intellectual disability; keto = ketogenic; LEV = levetiracetam; LOF = loss of function; MAE = myoclonic atonic epilepsy; max = maximum; OXC = oxcarbazepine; PEG = percutaneous endoscopic gastrostomy feeding tube; PHT = phenytoin; Reg = regions; Sp = spasms; sd = syndrome; STP = stiripentol; SUDEP = sudden unexpected death in epilepsy; SW = spike and slow waves; T = tonic; TCS = tonic-clonic seizures; TPM = topiramate; VPA = valproic acid.

causes of DEE (table 2 for an overview) and bear some similarity with those of *SCN2A* encephalopathy.[29] Cortical blindness has not been described in *SCN2A* encephalopathy but may be a common feature of severe encephalopathies with different etiologies.

During early childhood, 4 patients died in the context of profound neurologic deterioration and uncontrolled daily, prolonged seizures. Increased precocious death rate, because of SUDEP, has been reported[2,13,30,31] to occur in about 10% of patients with *SCN8A*.[12] Convulsive seizures leading to cardiac arrest and ultimately to SUDEP have been documented in a mouse model with a gain-of-function *SCN8A* mutation.[32–35]

In our cohort, we did not document "critical" ECG alterations during the seizures, whereas irregular breathing, cyanosis, and brady-/tachycardia were common. The prominent autonomic ictal manifestations and the prolonged seizure duration with frequent evolution to bilateral TCS may be risk factors for ictal death. However, none of these deaths were unexpected. Death occurred in early childhood, within a critical age (2–5 years) at which patients with *SCN8A*-DEE experience progressive worsening of their epilepsy and neurologic condition, rendering them susceptible to respiratory distress. Uncontrolled epilepsy, severe neurologic compromise, and the relentless severe infirmity likely contributed to the fatal outcome, suggesting that there are causes other than SUDEP for death in *SCN8A*-DEE.

Author contributions

E.G. conceived and designed the study, collected and analyzed data, and wrote the manuscript. R.S.M. was involved in study concept and design, collected and analyzed data and drafted/edited the manuscript. All the authors collected and analyzed data. R.G., I.E.S., K.B.H., G.R., S.R., F.C., C.M., M.P.F., B.K.B., M.T., S.S., P.V., S.B., and S.M. revised the manuscript.

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Disclosure

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